SUPPLEMENTAL DATA
A multicenter, open-label, phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors

Guy Young,[1*] Ri Liesner,[2] Tiffany Chang,[3] Robert Sidonio Jr.,[4] Johannes Oldenburg,[5] Victor Jiménez-Yuste,[6] Johnny Mahlangu,[7] Rebecca Kruse-Jarres,[8] Michael Wang,[9] Marianne Uguen,[10] Michelle Y Doral,[3] Lilyan Y Wright,[3] Christophe Schmitt,[10] Gallia G Levy,[3] Midori Shima,[11] and Maria Elisa Mancuso[12]

[1]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA; [2]Great Ormond Street Hospital, London, UK; [3]Genentech, Inc., South San Francisco, CA; [4]Emory University and Children's Healthcare of Atlanta, Atlanta, GA; [5]University of Bonn, Bonn, Germany; [6]Hospital Universitario La Paz, Autónoma University, Madrid, Spain; [7]University of the Witwatersrand and NHLS, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [8]Bloodworks Northwest, Seattle, WA; [9]University of Colorado Anschutz Medical Campus, Aurora, CO; [10]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [11]Nara Medical University, Kashihara, Japan; [12]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, Milan, Italy

Contents

* Corresponding author at gyoung@chla.usc.edu

Supplemental methods

HAVEN 2 participating institutions

Country	Institution	Principal investigator	Number of patients enrolled
United Kingdom	Great Ormond street Hospital for Children NHS Foundation Trust; Haemophilia Centre, London	Raina Liesner	10
United States	Children's Healthcare of Atlanta, Atlanta, Georgia	Robert Sidonio Jr.	9
Spain	Hospital Universitario la Paz; Servicio de Hematologia, Madrid	Victor Jiménez-Yuste	8
Germany	Universitätsklinikum Bonn; Institut für Experimentelle Hämatologie und Transfusionsmedizin, Bonn	Johannes Oldenburg	7
Italy	IRCCS Ca' Granda Ospedale Maggiore Policlinico; Centro Emofilia e Trombosi "Angelo Bianchi e Bonomi," Milan	Elena Santagostino	7
South Africa	Charlotte Maxeke Johannesburg Hospital; Haemophilia Comprehensive Care Center, Johannesburg	Johnny Mahlangu	6
United States	Children's Hospital Los Angeles, Los Angeles	Guy Young	5
Japan	Nara Medical University Hospital, Nara	Midori Shima	4
Turkey	Ege University, School of Medicine; Pediatrics Department, Izmir	Kaan Kavakli	3
Turkey	Istanbul University, Cerrahpasa Medical Faculty; Pediatrics Department, Istanbul	Bulent Zulfikar	3
United States	Bloodworks Northwest (formerly Puget Sound Blood Center), Seattle, Washington	Rebecca Kruse-Jarres	3
United States	University of Colorado Anschutz Medical Campus, Aurora, Colorado	Michael Wang	3
France	Groupe Hospitalier Necker Enfants Malades, Paris	Annie Harroche	2
		Chantal Rothschild*	
Japan	Shizuoka Children's Hospital, Shizuoka	Yasuo Horikoshi	2
Turkey	Adana Acibadem Hospital; Pediatric Hematology, Adana	Bulent Antmen	2
Spain	Hospital Universitario Virgen del Rocio; Servicio de Hematologia, Sevilla	Ramiro Nuñez	2
Spain	Hospital Universitario la Fe; Servicio de Hematologia, Valencia	Santiago Bonanad Boix	2
Costa Rica	ICIC, Detrás del Hospital México, San José	Willen Bujan	1
France	CH de Bicetre; Centre de Traitement d' Hemophilie, Le Kremlin-Bicêtre	Thierry Lambert	1

France	Hopital Cardio-vasculaire Louis Pradel; Hemostase clinique, Bron	Sandrine Meunier	1
Japan	Ogikubo Hospital, Tokyo	Takashi Suzuki	1
		Hideji Hanabusa*	
		Azusa Nagao	
Japan	Nagoya University Hospital, Nagoya	Tadashi Matsushita	1
Japan	Hospital of the University of Occupational and Environmental Health, Fukuoka	Koichi Oshida	1
		Rie Shirayama*	
United States	North Shore/Long Island Jewish PRIME; Pediatric Hematology/Oncology & Stem Cell Transplantation, New Hyde Park, New York	Suchitra Acharya	1
United States	Rush Medical Center, Chicago, Illinois	Mindy Simpson	1
United States	Children's Hospital of Michigan, Detroit, Michigan	Michael Callaghan	1
United States	Oregon Health & Science University, Department of Pediatrics, Portland, Oregon	Michael Recht	1

*Not a current investigator.

Trial registration

The HAVEN 2 study was registered at ClinicalTrials.gov on June 10, 2016. The first participant enrolled on July 22, 2016.

Full inclusion criteria

Participants had to meet the following criteria for study entry:

- Children <12 years of age at the time of informed consent with allowance for the following:
  - participants 12–17 years of age who weighed <40 kg at the time of informed consent
  - participants <2 years of age were allowed to participate only after the protocol-defined interim data review criteria were met
- Body weight >3 kg at time of informed consent
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures including the completion of applicable patient-reported outcome questionnaires
- Caregivers of all children must have had the willingness and ability to comply with all study procedures including the completion of the Bleed and Medication Questionnaire (BMQ) and applicable health-related quality of life questionnaires
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (ie, ≥5 BU/mL)
- Treatment with bypassing agents
- For participants ≥2 years of age:
  - if on an episodic bypassing agent regimen: the annualized bleeding rate of ≥6 (eg, 3 bleeds in the last 24 weeks) OR
  - if on a prophylactic bypassing agent regimen: inadequately controlled (eg, 2 bleeds since starting prophylaxis or 1 life-threatening bleed) or central venous access device (CVAD) placement medically not feasible or deemed unsafe by the investigator
- For participants <2 years of age: determined by the investigator to be in high unmet medical need
- Adequate hematological function, defined as a platelet count of ≥100×10^9 cells/L and hemoglobin ≥8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤1.5× age-adapted upper limit of normal (ULN) (excluding Gilbert's syndrome) and *both* aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3× age-adapted ULN at the time of screening
- Adequate renal function: serum creatinine of ≤1.5× ULN for age. When the serum creatinine was ≥1.5× ULN, creatinine clearance by Bedside Schwartz formula of >70 mL/min/1.73 m^2.

Full exclusion criteria

Children who met any of the following criteria were excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or planned to receive during the study) immune tolerance induction (ITI) therapy or prophylaxis treatment with factor VIII
  - participants awaiting initiation of ITI were eligible

  - participants in whom ITI had failed were eligible with a 72-hour washout period prior to the first emicizumab administration
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other diseases (ie, certain autoimmune diseases [eg, systemic lupus erythematosus], cardiovascular disease) that may increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known infection with HIV, hepatitis B virus (HBV), hepatitis C virus (HCV)
- Participants at high risk for thrombotic microangiopathy (TMA) (eg, with a previous medical or family history of TMA), in the investigator's judgment
- Use of systemic immune-modulators (eg, interferon or corticosteroids) at enrollment, or planned use during the study period
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of:
  - an investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
  - a non–hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
  - an investigational drug concurrently
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or sponsor, preclude safe participation in and completion of the study or interpretation of the study results.

Permitted concomitant therapies

Concomitant use of the following drugs and therapies was permitted:

- Drugs intended to control or prevent bleeds, including recombinant factor VIIa and activated prothrombin complex concentrate (aPCC), could be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab increases participants' coagulation potential, the doses required to achieve hemostasis may be lower than the bypassing agent doses used prior to starting the study
- Caution was required for participants using recombinant factor VIIa (eg, consideration of using ≤90 µg/kg as an initial dose)
- Use of aPCC in combination with emicizumab was to be entirely avoided in participants who had the option of using other bypassing agents to treat bleeds. In the event that aPCC was the only available bypassing agent, the lowest dose expected to achieve hemostasis was to be prescribed, with ≤50 U/kg of aPCC to be administered as an initial dose
- Other bypassing agents (eg, Byclot®) were to be avoided. In cases where such agents were the only available bypassing agent, the lowest dose expected to achieve hemostasis was to be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (eg, ≤60 µg/kg of Byclot®)
- Exact dose and schedule of bypassing agents were to be discussed with caregivers at the beginning and throughout the study. Repeated dosing of recombinant factor VIIa, aPCC, or other bypassing agents was to be performed only under medical supervision

and consideration given to verifying bleeds prior to repeated dosing. For recombinant factor VIIa, aPCC, and other bypassing agents, laboratory monitoring by additional local and central laboratory assessments was to be performed as per the schedule of assessments

- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure
- Local anesthetic cream for emicizumab subcutaneous administration
- Vaccinations were to be administered following national immunization schedules. As per the World Federation of Hemophilia (WFH) recommendations for vaccinations, participants with hemophilia should be vaccinated. Thus, injections were to be administered according to the WFH recommendations and local Hemophilia Treating Center practice and ideally during a period when the bleeding status of the child was well controlled and stable. Vaccinations could not be administered on the same day as an emicizumab administration but ideally at a timepoint between 2 emicizumab administrations (>48 hours after emicizumab administration). Children who received vaccinations were carefully followed for any adverse reactions in the subsequent days following vaccine administration
- Caution was to be taken if antifibrinolytics were used in conjunction with recombinant factor VIIa in participants receiving emicizumab.

Prohibited concomitant therapies

Use of the following therapies was prohibited during the study and for ≥4 weeks prior to initiation of study treatment:

- Use of aPCC or Byclot® as a concomitant prophylactic treatment, including for short-term prophylaxis
- Use of concomitant prophylactic regimen with factor VIII or recombinant factor VIIa
  - intermittent doses or short-term prophylaxis (eg, around the time of surgery), however, were permitted
- Use of drugs that would affect hemostasis or platelet function (eg, aspirin, nonsteroidal anti-inflammatory drugs that are not selective or preferential COX-2 inhibitors, or anticoagulants [other than to flush, dwell, or de-clot a CVAD]) but excluding medications intended to control bleeding episodes or used in the context of minor surgery (eg, tooth extraction) or injuries (eg, concussion) to prevent deterioration
- Use of systemic immunomodulators (eg, rituximab, corticosteroids) other than antiretroviral therapy
- Elective surgery (excluding minor procedures such as tooth extraction, CVAD removal, incision and drainage, as well as emergency surgeries)
- Use of other investigational drugs
- Use of antifibrinolytics in conjunction with aPCC or Byclot®
- If prohibited therapy was administered for any reason, it was recorded on the electronic case report form (except for any hemophilia-related medication, which was recorded on the BMQ). If prohibited treatment was prescribed or considered medically necessary, the Medical Monitor had to be consulted to discuss any changes in the benefit/risk profile and determine whether the participant should continue on the study.

Target joint analysis

Target joints were defined as a major joint (eg, hip, elbow, wrist, shoulder, knee, ankle) into which ≥3 bleeds occur over a 24-week period. At study entry, the presence of target joints based on bleeds in the 24 weeks prior to enrollment was recorded. In a post-hoc analysis (not predefined in the Statistical Analysis Plan), in participants who reported target joints at baseline, target joint resolution was defined as ≤2 bleeding events within any consecutive 52-week period during emicizumab treatment.

Antidrug antibodies (ADAs)

Anti-emicizumab antibodies were measured in plasma as per the schedule of assessments using a validated bridging enzyme-linked immunosorbent assay (ELISA). Samples were collected at trough emicizumab concentrations. The analysis was performed by QPS Netherlands B.V. (Groningen, Netherlands). The ELISA had a sensitivity of 6.04 ng/mL. The precision (% coefficient of variation [CV]) of the positive control samples ranged between 3.8% and 5.9% for screening assay runs.

Data on the impact of ADAs on safety, efficacy, and/or pharmacokinetics and pharmacodynamics were summarized using standard language/terminology.[1] In the absence of a neutralizing antibody assay, ADAs associated with consistent decline of emicizumab exposure (corroborated by associated loss of pharmacodynamic effect) were considered as having a neutralizing potential.

To identify ADAs with neutralizing potential, the pharmacokinetic profiles of participants with ADAs were visually inspected to identify those where the observed pharmacokinetic profile declined relative to the expected profile, as observed for each of the dosing regimens (including a potential dose uptitration). Additionally, this decline had to be consistent over time (ie, must have been observed at >1 timepoint). This pharmacokinetic-based evaluation was further corroborated/supported by the assessment of corresponding pharmacodynamic profiles (factor VIII activity using a chromogenic assay containing human coagulation factors [BIOPHEN™ Factor VIII; Hyphen Biomed, Neuville sur Oise, France], and in a less sensitive manner activated partial thromboplastin time [aPTT; STA-PTT A; Diagnostica Stago, Asnières sur Seine, France]). All pharmacodynamic biomarker analyses were performed by Medpace Reference Laboratories (Cincinnati, OH).

Supplemental results

Efficacy in participants aged ≤2 years receiving emicizumab prophylaxis

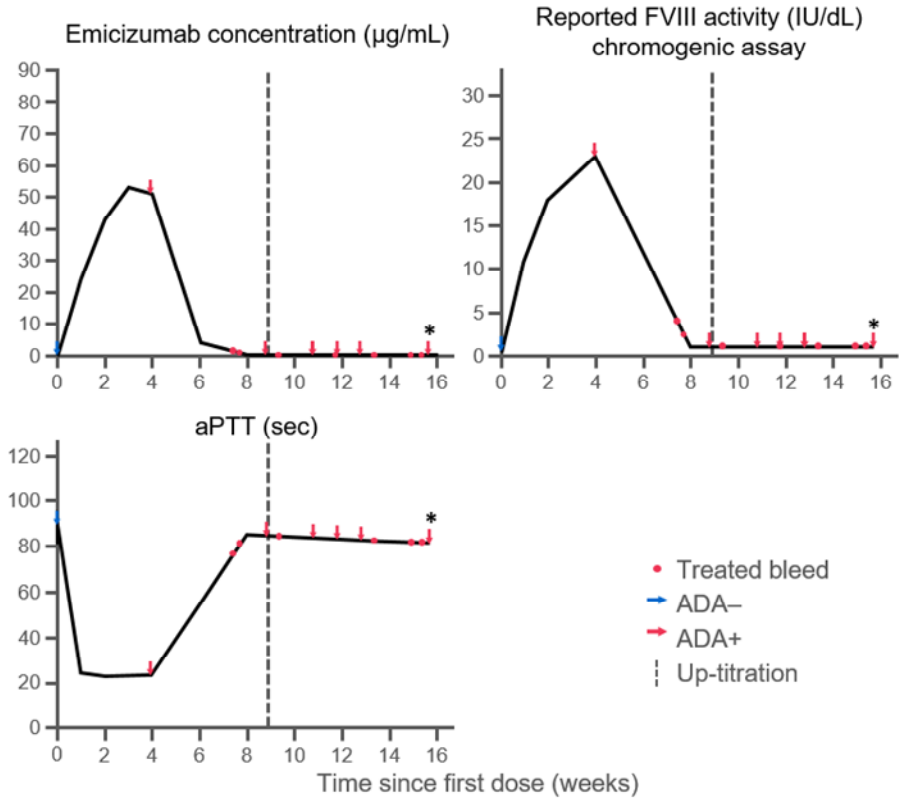
Among the 18 participants aged ≤2 years, with a median (range) efficacy period of 39.0 (17.9–56.9) weeks, a total of 16 bleeds were reported, only 2 of which were treated bleeds (both traumatic, 1 on the forehead, 1 on the mouth). No participant experienced a treated joint bleed, treated target joint bleed, or a treated spontaneous bleed.

Immunogenicity

Four of 88 participants tested positive for ADAs (4.5%), all of which were treatment-induced. The development of ADAs was not associated with any adverse events, such as systemic hypersensitivity reactions or injection-site reactions. Two participants had ADAs with neutralizing potential based on declining pharmacokinetics and corresponding pharmacodynamics (see supplemental Methods). One withdrew from treatment due to lack of efficacy; the second continued on study without bleeding events and was ADA-negative 48 weeks after the initial detection of ADAs. These 2 ADA cases are detailed below.

Case 1

One case of ADAs with neutralizing potential occurred in a participant in group C and was reported as a serious adverse event. The development of ADAs in this participant was not associated with observable toxicity, such as systemic hypersensitivity reactions. In this participant, ADAs were detected near the end of the loading dose period (week 5). A sharp decline in emicizumab concentration and factor VIII activity measured by the human chromogenic assay, together with aPTT prolongation, were observed after this timepoint (see figure below). Results confirmed the presence of antidrug antibodies at week 5 and week 9, prior to 6 mg/kg emicizumab administration. Due to suspected neutralizing ADAs, the participant was permitted a trial of uptitration to 3 mg/kg every week (starting at week 9) in an attempt to overcome the ADAs. No improvement in pharmacokinetics or pharmacodynamics following uptitration was observed. However, since the ADAs developed during the loading period when the participant was receiving 3 mg/kg every week, uptitration would not be expected to successfully overcome the ADAs. Weeks 9 through 16, emicizumab trough concentration declined to undetectable levels, and factor VIII activity dropped to ~1%. In the absence of emicizumab, aPTT reverted to baseline values. The participant discontinued emicizumab treatment due to lack of efficacy.

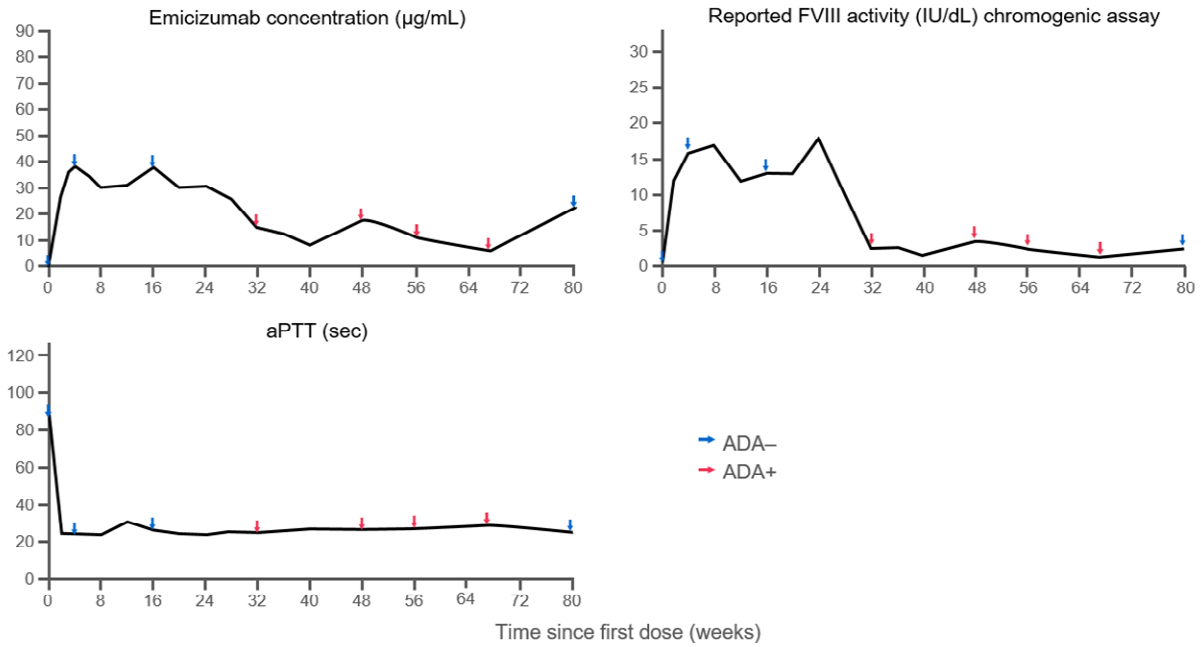


ADA, antidrug antibody; aPTT, activated partial thromboplastin time.

*Sample confirmed positive after the initial snapshot.

Case 2

The second participant was enrolled in group A. ADAs were first detected at week 32. The participant had pharmacokinetic and pharmacodynamic profiles indicative of ADAs with neutralizing potential (see figure below). At the time of data cut-off, this participant had not experienced any bleeding event and remained on study at the initial emicizumab dose of 1.5 mg/kg per week. Spontaneous resolution of ADA with recovery of pharmacokinetic parameters was seen 48 weeks after initial ADA detection.



ADA, antidrug antibody; aPTT, activated partial thromboplastin time.

Supplemental tables

Table 1. Type and location of treated bleeds in participants <12 years old treated with emicizumab 1.5 mg/kg per week

	Group A: Emicizumab once weekly (n = 65)
Bleeds, n	22
Spontaneous, n (%)	2 (9.1)
Traumatic, n (%)	20 (90.9)
Joint	
Participants, n	10
Bleeds, n (%)	12 (54.5)
Ankle, n (%)	8 (66.7)
Elbow, n (%)	0
Knee, n (%)	2 (16.7)
Fingers/thumb, n (%)	1 (8.3)
Toes, n (%)	1 (8.3)
Muscle	
Participants, n	3
Bleeds, n (%)	3 (13.6)
Thigh, n (%)	2 (66.7)
Calf, n (%)	1 (33.3)
Upper arm, n (%)	0
Other	
Participants, n	7
Bleeds, n (%)	7 (31.8)
Forehead, n (%)	3 (42.9)
Foot, n (%)	1 (14.3)
Hip, n (%)	1 (14.3)
Mouth, n (%)	1 (14.3)
Thigh, n (%)	1 (14.3)

Table 2. Summary of adverse events with >10% incidence reported in all participants treated across all 3 dosing regimens

Adverse event >10% incidence n (%)	**Total participants (n = 88)**
Nasopharyngitis	33 (37.5)
Injection-site reaction*	27 (30.7)
Pyrexia	21 (23.9)
Upper respiratory tract infection	21 (23.9)
Cough	21 (23.9)
Diarrhea	14 (15.9)
Vomiting	14 (15.9)
Headache	13 (14.8)
Contusion	11 (12.5)
Fall	11 (12.5)
Influenza	9 (10.2)

*No participant discontinued due to injection-site reactions.

Table 3. Observed bleeding rates in prospective pediatric studies of FVIII prophylaxis

FVIII prophylaxis	Product type	Frequency of IV administration	Number of pediatric pts	Mean ABR (95% CI or ±SD)	Median ABR (IQR or range)	% Pts with zero bleeds	Ratio of pts with zero target joints‖	Reference
Advate® (Shire)	Standard: Octocog alfa (recombinant)	Q2D	46 (1–6 y)	—	3.1 (0.4–6.6)†	24	—	USPI
			47 (10–17 y)	—	3.3 (1.1–6.6)†	17	—	Fischer et al 2011[2]
			3 (7–11 y)	—	5.2	33	—	
			4 (12–15 y)	—	5.0	25	—	
NovoEight® (Novo Nordisk)	Standard: Turoctocog alfa (recombinant)	3×/week or Q2D	63 (0–11 y)	5.3 (3.9–7.3)	3.0 (8.5)	—	—	USPI Kulkarni et al 2013[3]
Nuwiq® (Octapharma)	Standard: Simoctocog alfa (recombinant)	3×/week or Q2D	49 (2–12 y)	2.9 (±4.7)	1.7 (0.0–27.8)‡	34§	—	USPI Klukowska et al 2016‡ & 2018[4,5]
Kovaltry® (Bayer)	Standard: Octocog alfa (recombinant)	2×–3×/week or Q2D	51 (0–11 y)	3.8 (±5.0)	1.9 (0.0–6.0)†	45	—	USPI Ljung et al 2016[6]
Afstyla® (CSL Behring)	Standard: Lonoctocog alfa (recombinant), single chain	2×–3×/week	80 (0–11 y)	5.5 (4.8–6.3)	3.7 (0.0–7.2)†	26.3	—	USPI Al-salama and Scott, 2017; Stasyshyn et al 2017[7,8]
Eloctate® (Bioverativ)	Extended half-life: Efmoroctocog alfa (recombinant), Fc fusion protein	2×/week	69 (0–11 y)	—	2.0 (0.0–4.0)	46.4	— —	USPI Young et al 2015[9]
Adynovate® (Shire)	Extended half-life: Rurioctocog alfa pegol (recombinant), PEGylated	2×/week	66 (0–11 y)	3.0 (2.2–4.2)	2.0 (0.0–3.9)†	38.0	8/14 (57.1%)	USPI Mullins et al 2017[10]
Jivi® (Bayer)	Extended half-life:	2×/week, Q5D, or QW	32 (<6 y)	—	2.7 (1.1–6.8)†	29.1	—	Santagostino et al 2016[11]
			28 (6–11 y)	—	2.9 (0–6.7)†	28.6	—	

	Antihemophilic factor (recombinant), PEGylated		60 (0–11 y)	—	2.9 (0.5–6.8)†	25.0	—	
N8-GP* (Novo Nordisk)	Extended half-life: Turoctocog alpha pegol (recombinant), glycoPEGylated	2×/week	68 (0–11 y)	2.1 (1.5–3.0)	1.9 (0–2.8)	42.6	15/19 (79.9%)	Meunier et al 2017[12]

*Not an approved therapy.

†IQR reflects the first quartile and third quartile.

‡Data are IQR (range).

§In a group of 59 pediatric participants ages 2–12 years (Klukowska et al 2016).

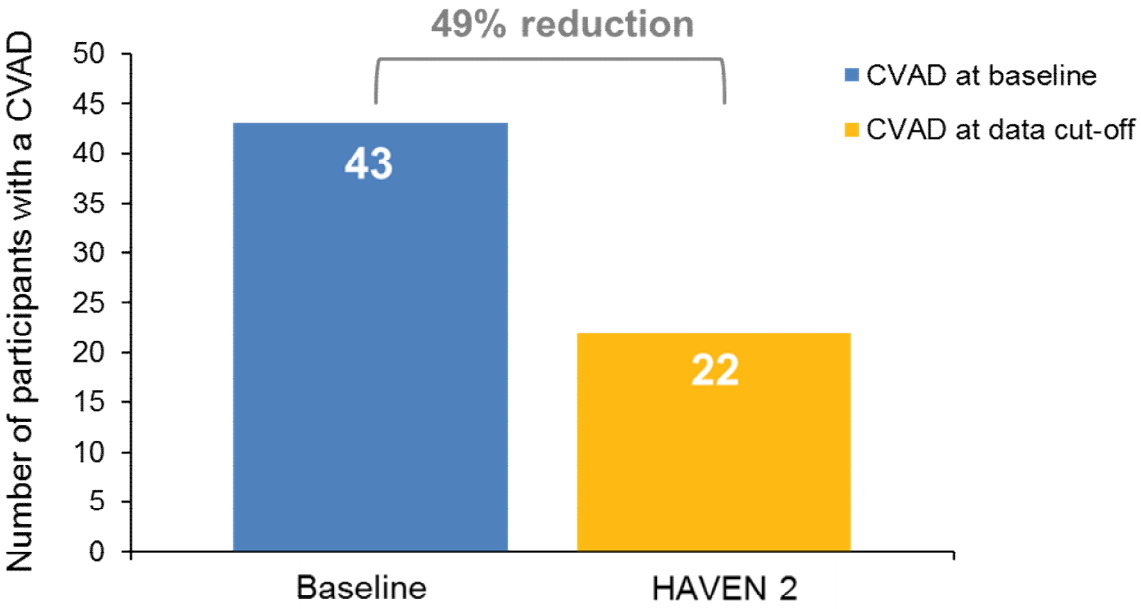
‖Target joints are defined as joints with ≥3 bleeding episodes in the same joint within a 6-month period. The ratio of participants without target joints after treatment vs participants with target joints at baseline. Percentage of participants with target joints at baseline who had no target joints after treatment.

Em-dash indicated data not available in the reference cited.

ABR indicates annualized bleeding rate; CI, confidence interval; FVIII, factor VIII; IQR, interquartile range; IV, intravenous; pts, patients; Q2D, every 2 days; Q5D, every 5 days; QW, once weekly; SD, standard deviation; and USPI, US prescribing information.

Supplemental figures

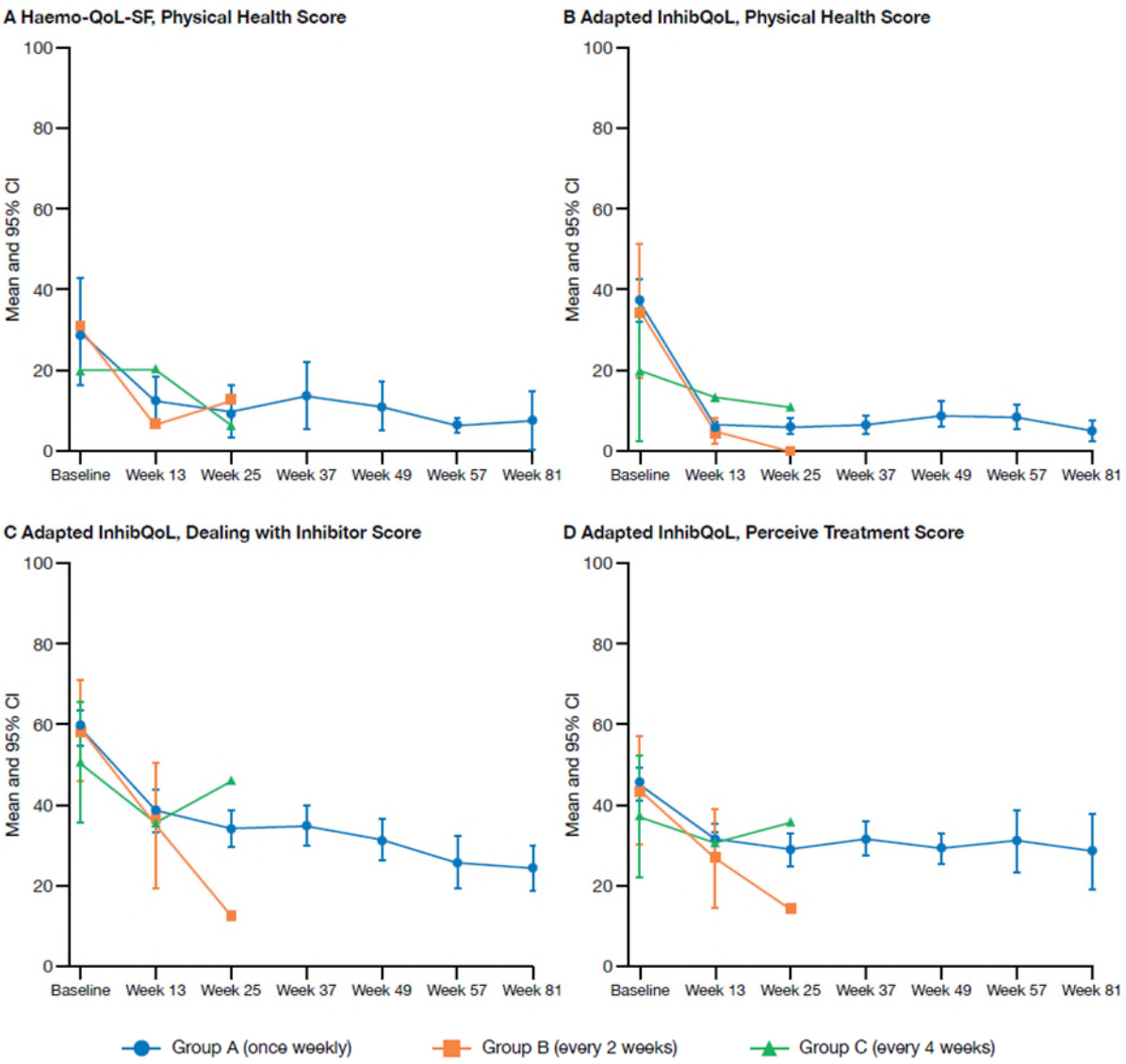
Figure 1. Proportion of participants with CVAD removals during the study



Data cut-off: October 9, 2018. (This date, which is ~5 months after the clinical cut-off date for the primary analysis, was selected for this post-hoc analysis because a number of participants underwent CVAD removal between April and October.)

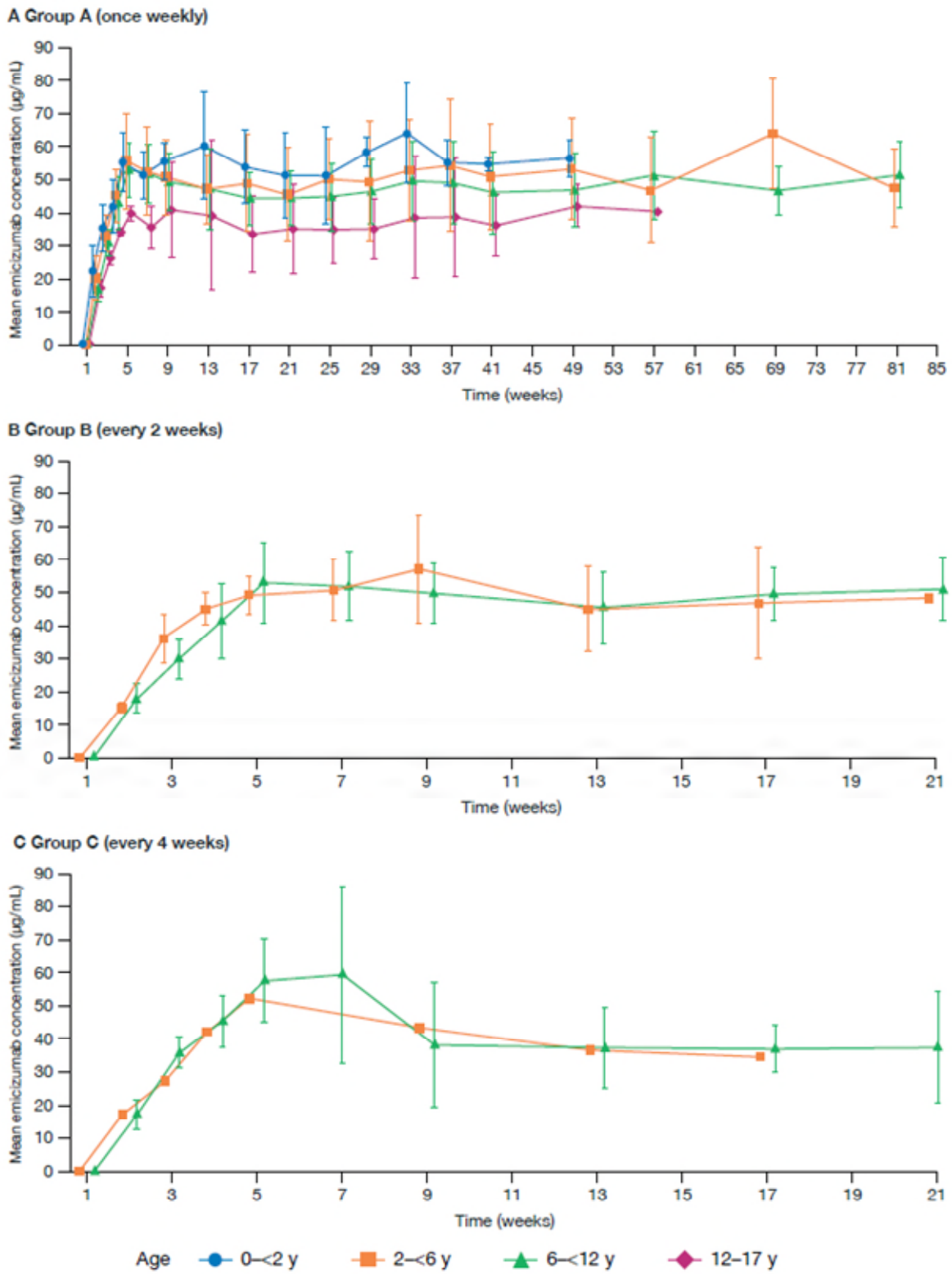
CVAD, central venous access device.

Figure 2. Quality of life of participants receiving emicizumab prophylaxis



CI, confidence interval; Haemo-QoL-SF, Haemophilia-Quality of Life-Short Form; Inhib-QoL, Health-Related Quality of Life in Haemophilia Patients with Inhibitors.

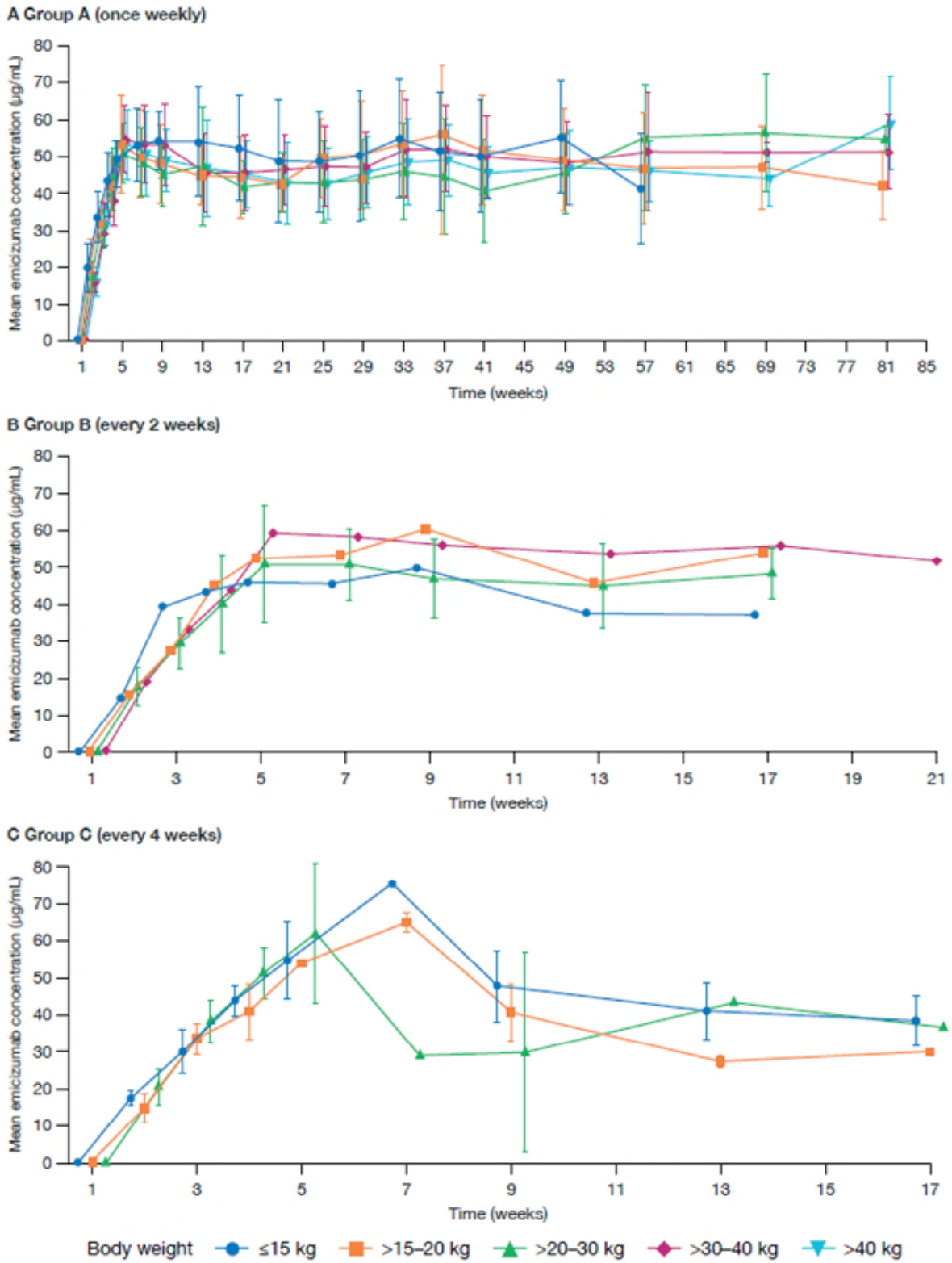
Figure 3. Mean (SD) emicizumab plasma concentrations by age category



All timepoints display trough plasma concentration except week 7 for group C, which displays peak plasma concentration.

SD, standard deviation.

Figure 4. Mean (SD) emicizumab plasma concentrations by body weight category



All timepoints display trough plasma concentration except week 7 for group C, which displays peak plasma concentration.

SD, standard deviation.

References

1. Shankar G, Arkin S, Cocea L, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. *AAPS J.* 2014;16(4):658-673.
2. Fischer K, Collins P, Bjorkman S, et al. Trends in bleeding patterns during prophylaxis for severe haemophilia: observations from a series of prospective clinical trials. *Haemophilia.* 2011;17(3):433-438.
3. Kulkarni R, Karim FA, Glamocanin S, et al. Results from a large multinational clinical trial (guardian™3) using prophylactic treatment with turoctocog alfa in paediatric patients with severe haemophilia A: safety, efficacy and pharmacokinetics. *Haemophilia.* 2013;19(5):698-705.
4. Klukowska A, Szczepanski T, Vdovin V, et al. Long-term tolerability, immunogenicity and efficacy of Nuwiq® (human-cl rhFVIII) in children with severe haemophilia A. *Haemophilia.* 2018;24(4):595-603.
5. Klukowska A, Szczepański T, Vdovin V, Knaub S, Jansen M, Liesner R. Novel, human cell line-derived recombinant factor VIII (Human-cl rhFVIII, Nuwiq®) in children with severe haemophilia A: efficacy, safety and pharmacokinetics. *Haemophilia.* 2016;22(2):232-239.
6. Ljung R, Kenet G, Mancuso ME, et al. BAY 81-8973 safety and efficacy for prophylaxis and treatment of bleeds in previously treated children with severe haemophilia A: results of the LEOPOLD Kids Trial. *Haemophilia*. 2016;22(3):354-360.
7. Al-Salama ZT, Scott LJ. Lonoctocog Alfa: A review in haemophilia A. *Drugs.* 2017;77(15):1677-1686.
8. Stasyshyn O, Djambas Khayat C, Iosava G, et al. Safety, efficacy and pharmacokinetics of rVIII-SingleChain in children with severe hemophilia A: results of a multicenter clinical trial. *J Thromb Haemost*. 2017;15(4):636-644.
9. Young G, Mahlangu J, Kulkarni R, et al. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *J Thromb Haemost*. 2015;13(6):967-977.
10. Mullins ES, Stasyshyn O, Alvarez-Román MT, et al. Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A. *Haemophilia.* 2017;23(2):238-246.
11. Santagostino E SK, Kenet G, Fischer K, Biss T, Radke S, Michaels L.A. PROTECT VIII kids trial results: BAY 94-9027 safety and efficacy in previously treated children with severe hemophilia A. 32nd International Congress of the World Federation of Hemophilia. Orlando, FL, USA 2016.
12. Meunier S, Alamelu J, Ehrenforth S, et al. Safety and efficacy of a glycoPEGylated rFVIII (turoctocog alpha pegol, N8-GP) in paediatric patients with severe haemophilia A. *Thromb Haemost.* 2017;117(9):1705-1713.